

## SUPPLEMENTARY FIGURE LEGENDS

**Figure S1 Differential genome-wide coverage of MBDCap sequence reads.** Data was arcsine-square-root-transformed to help visualize low coverage regions. Rows and columns represent chromosomal segments and sample methylation profiles, respectively. Row heights are normalized relative chromosome-wide CpG density. Boxes highlight significant tissue phenotypes that had the highest mean sequence coverage for a genomic feature within a chromosome. TPM, transcripts per million. Circles,  $P < 0.05$ ; Stars,  $P < 0.01$ .  $P$ -values were from Kruskal-Wallis tests.

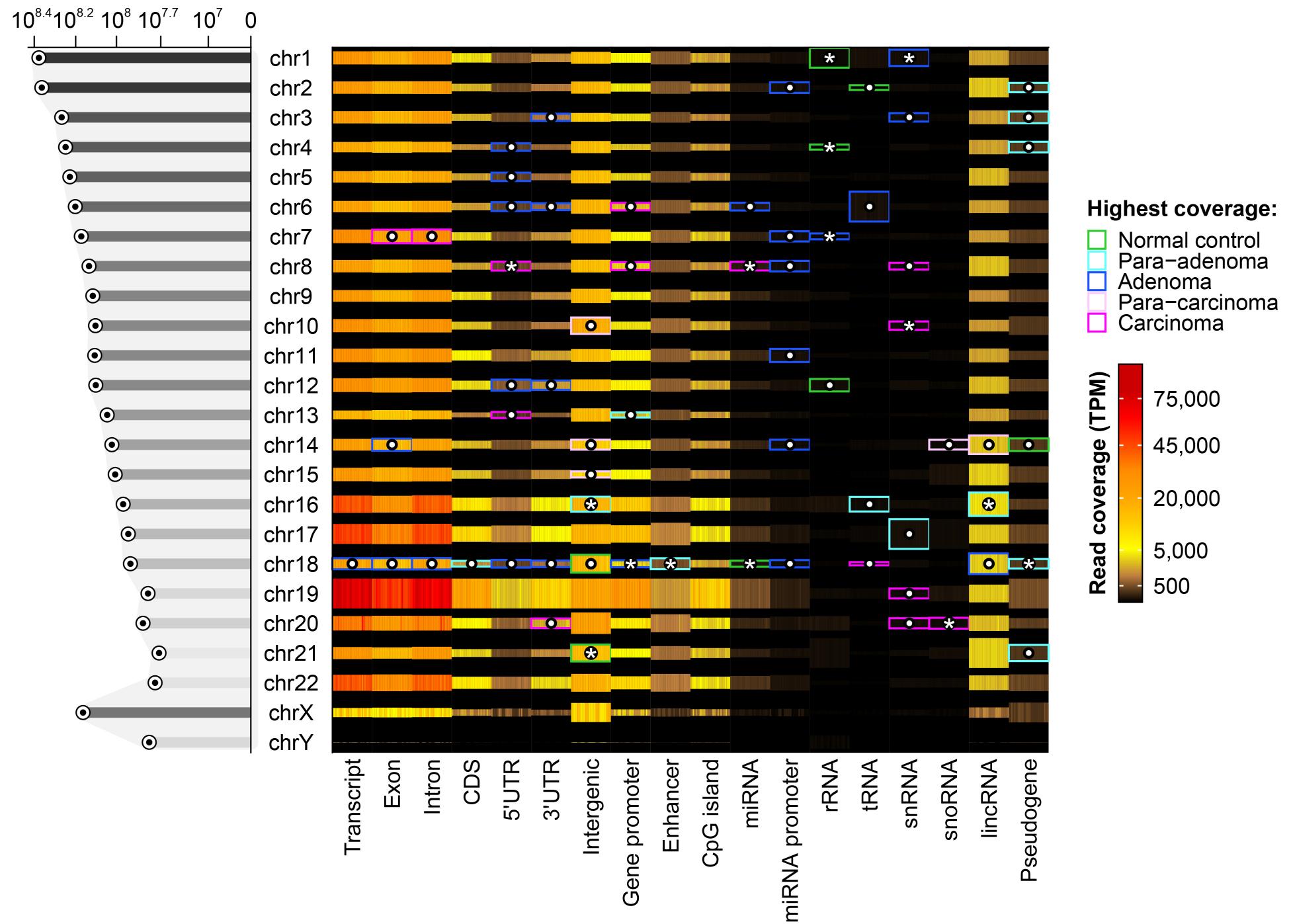
**Figure S2 Differentially methylated regions (DMRs) in colorectal carcinogenesis.** Of the 1,059 representative DMRs identified, 465 (43.9%) were annotated with HGNCs; this subset of segments was assigned to promoter regions (96 or 20.6%) in which CpG islands were present (48 or 50%). Rows and columns represent genomic segments and sample DMR profiles, respectively.

**Figure S3 Heatmap of bacteria abundances in phenotype groups.** From left to right the bacteria abundances are displayed in groups of normal, adenoma adjacent (AN), adenoma, CRC AN, and CRC. From top to bottom the bacteria are ranked by the fold-change between CRC and CRC AN samples. The bacteria shown are the ones with differential abundance between any two phenotype groups ( $P < 0.2$ ).

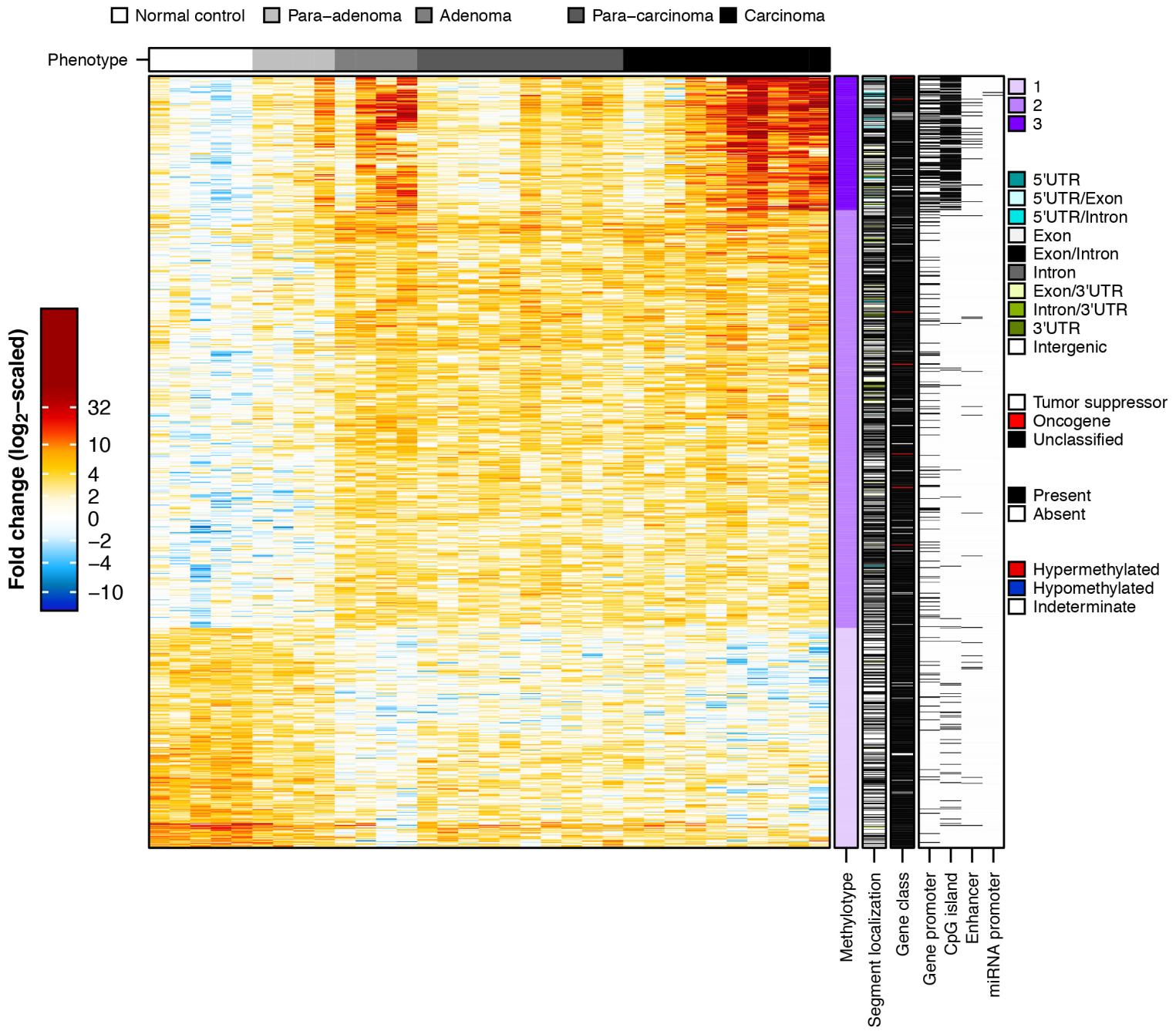
**Figure S4 Induction of prostaglandin E<sub>2</sub> biosynthetic pathway by *H. hathewayi*.** Expression of *Pla2g4c* and *Cox2* in colonic epithelium of mice gavaged with or without *H. hathewayi* was quantified by RT-qPCR. Expression levels were compared using *t*-test. \*,  $P < 0.05$ ; \*\*  $P < 0.01$  significantly different between the indicated groups.

**Figure S1**

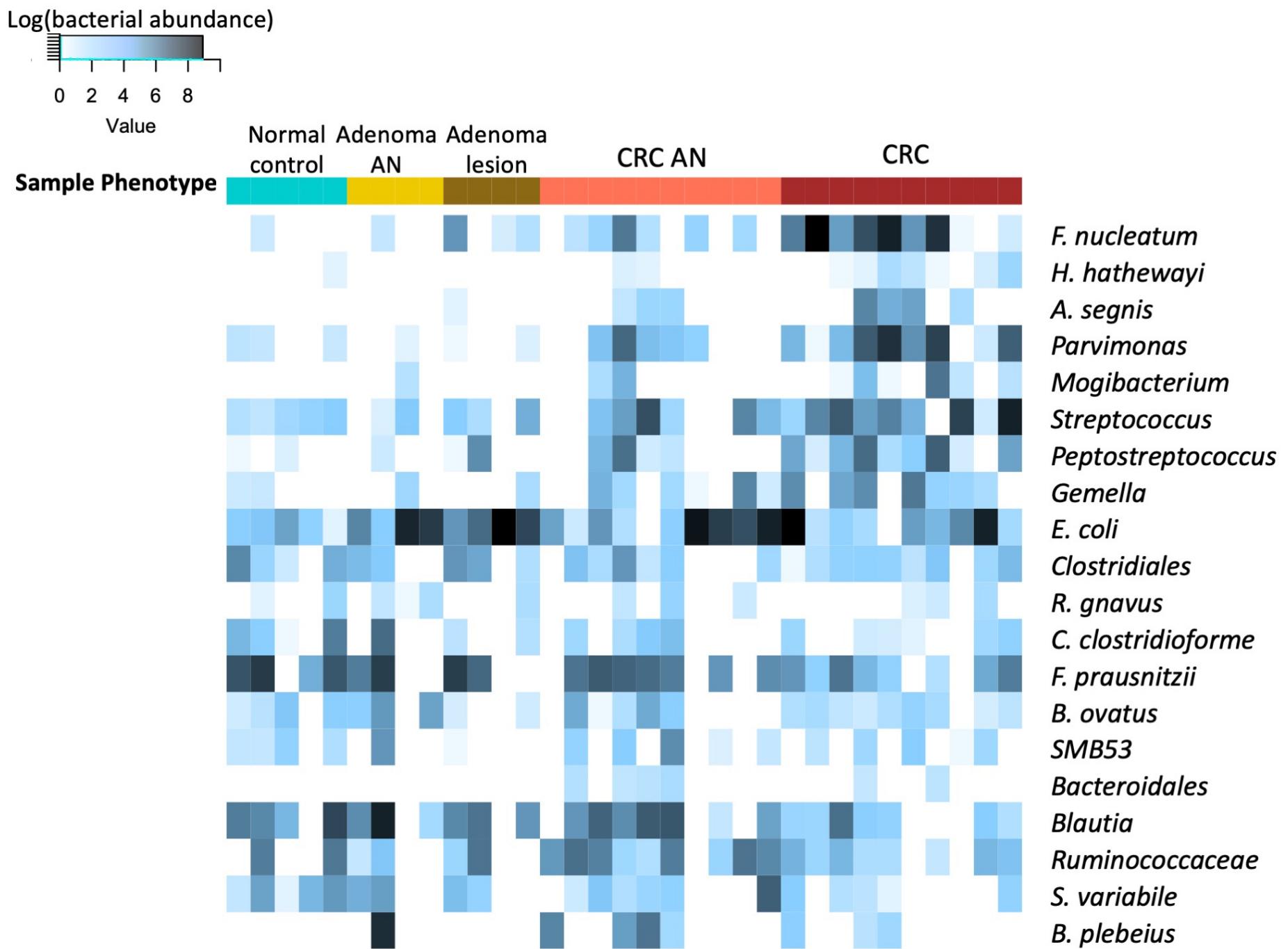
Total assembly length (bps)



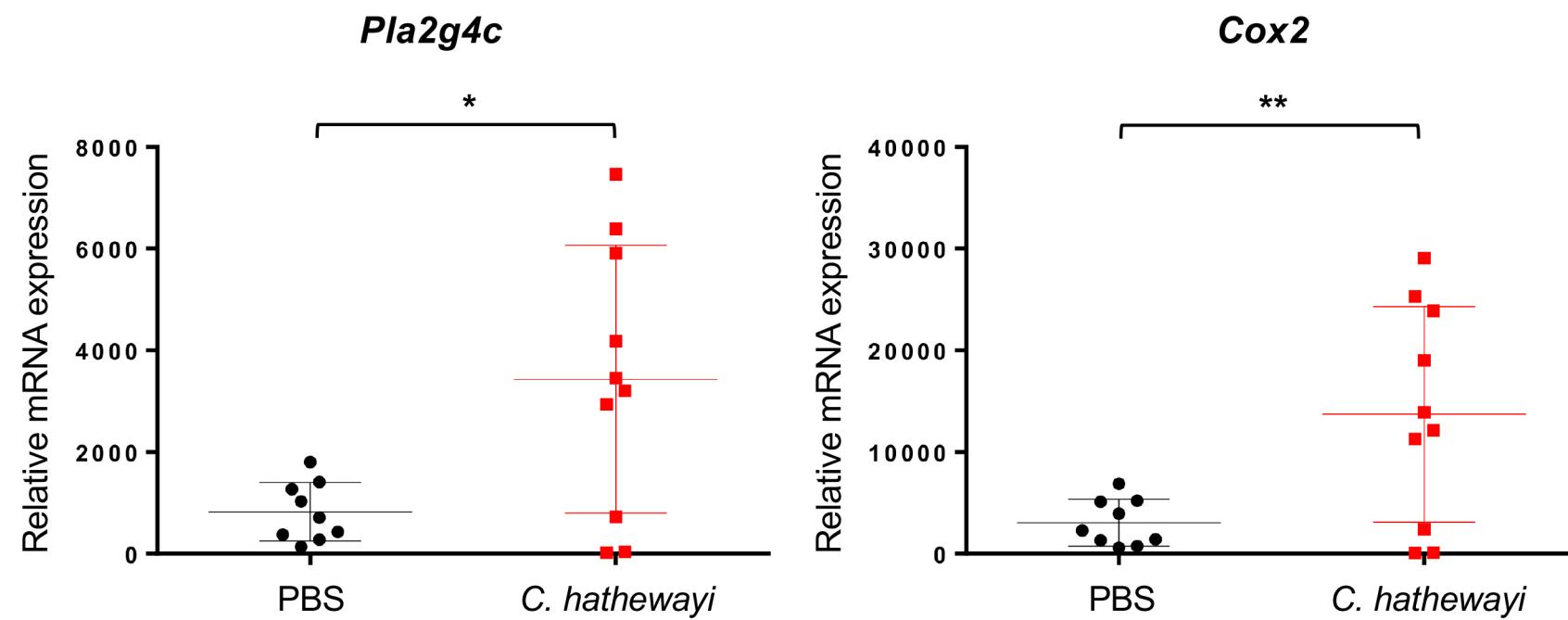
**Figure S2**



**Figure S3**



**Figure S4**



**Supplementary Table 1.** Top bacteria-methylation interactions of *C. hathewayi* and *F. nucleatum* with tumor suppressor genes.

Bacteria	Methylation Segment	Gene	ZINB <sup>1</sup> Beta	Beta P-value	Spearman Rho	Rho P-value <sup>2</sup>
<i>C. hathewayi</i>	chr2_5693962	<b><i>SOX11</i></b>	4.22	1.71E-05	0.38	0.030
	chr20_23049391	<b><i>THBD</i></b>	1.43	6.77E-07	0.11	0.029
	chr4_153788818	<b><i>SFRP2</i></b>	1.57	1.16E-05	0.38	0.029
	chr20_62475232	<b><i>GATA5</i></b>	1.46	9.52E-05	0.17	0.030
	chr6_133240654	<b><i>EYA4</i></b>	1.12	3.85E-05	0.22	0.119
	chr6_151807657	<b><i>ESRI</i></b>	1.33	2.50E-04	0.17	0.103
<i>F. nucleatum</i>	chr8_124562803	<b><i>MTSSI</i></b>	6.47	1.54E-06	0.44	0.011
	chr20_57393064	<b><i>RBM38</i></b>	3.45	6.35E-05	0.48	0.005
	chr20_57392518	<b><i>RBM38</i></b>	1.95	1.93E-06	0.44	0.010
	chr16_2107561	<b><i>PKD1</i></b>	7.56	6.47E-04	0.48	0.005
	chr6_133242292	<b><i>EYA4</i></b>	2.19	5.59E-04	0.44	0.010
	chr6_133241200	<b><i>EYA4</i></b>	1.53	3.98E-04	0.47	0.006
	chr20_43189420	<b><i>PTPRT</i></b>	1.96	3.79E-04	0.39	0.026

1. ZINB: Zero-Inflated Negative Binomial Regression. ZINB Beta: the beta in the count model of ZINB. *P*-value threshold < 0.001.

2. Spearman rank correlation test. *P*-value threshold < 0.15.

**Supplementary Table 2.** The positive significant (ZINB  $p$ -value  $\leq 0.05$ ) interactions of *MLH1*, *APC*, *PTEN*, *P16*, *CDX1* and *CDX2* with bacteria.

Gene	Methylation	Bacteria	ZINB	ZINB	Spearman	Rho
	Segment		Beta	P-value	Rho	P-value
<i>MLH1</i>	<i>chr3_36995323</i>	<i>Streptococcus.spp</i>	10.01	4.41E-06	0.24	0.19
	<i>chr3_36993412</i>	<i>A. segnis</i>	2.12	9.29E-04	0.08	0.64
	<i>chr3_37009792</i>	<i>F. nucleatum</i>	3.45	1.22E-03	0.29	0.10
	<i>chr3_37026718</i>	<i>Streptococcus.spp</i>	5.48	7.96E-03	0.03	0.87
	<i>chr3_37026991</i>	<i>C. clostridioforme</i>	18.10	1.01E-02	0.21	0.24
	<i>chr3_36994231</i>	<i>Streptococcus.spp</i>	1.65	1.08E-02	0.28	0.12
	<i>chr3_37010065</i>	<i>F. nucleatum</i>	6.54	1.40E-02	0.15	0.42
	<i>chr3_36993685</i>	<i>Ruminococcaceae</i>	2.21	2.17E-02	0.32	0.07
	<i>chr3_37026718</i>	<i>F. nucleatum</i>	7.21	2.38E-02	0.04	0.81
	<i>chr3_37026445</i>	<i>C. clostridioforme</i>	3.53	2.67E-02	0.25	0.16
	<i>chr3_37012795</i>	<i>C. hathewayi</i>	6.55	2.69E-02	0.10	0.56
	<i>chr3_37010611</i>	<i>Ruminococcaceae</i>	4.64	3.35E-02	0.09	0.62
	<i>chr3_36993412</i>	<i>Ruminococcaceae</i>	1.89	3.68E-02	0.24	0.18
	<i>chr3_36995050</i>	<i>B. plebeius</i>	6.89	4.26E-02	0.33	0.06
<i>APC</i>	<i>chr3_36995323</i>	<i>Parvimonas.spp</i>	6.94	4.53E-02	0.06	0.74
	<i>chr3_36994231</i>	<i>C. hathewayi</i>	2.11	4.60E-02	0.06	0.75
	<i>chr3_37026445</i>	<i>Streptococcus.spp</i>	1.63	4.98E-02	0.07	0.70
	<i>chr5_112737808</i>	<i>C. hathewayi</i>	1.11	2.26E-05	0.11	0.54
	<i>chr5_112736443</i>	<i>B. plebeius</i>	7.69	2.29E-04	0.27	0.14
	<i>chr5_112738081</i>	<i>C. hathewayi</i>	4.74	3.14E-04	0.20	0.28
	<i>chr5_112707232</i>	<i>A. segnis</i>	3.23	3.98E-04	0.11	0.53
	<i>chr5_112778485</i>	<i>C. clostridioforme</i>	2.69	6.71E-04	0.05	0.80
	<i>chr5_112825441</i>	<i>Peptostreptococcus</i>	4.91	1.06E-03	0.09	0.60
	<i>chr5_112778485</i>	<i>B. plebeius</i>	3.34	1.75E-03	0.25	0.16
	<i>chr5_112736443</i>	<i>F. nucleatum</i>	3.95	2.73E-03	0.19	0.28
	<i>chr5_112707232</i>	<i>Ruminococcaceae</i>	1.58	4.93E-03	0.10	0.60
	<i>chr5_112738081</i>	<i>Streptococcus.spp</i>	2.67	8.20E-03	0.14	0.43
	<i>chr5_112738081</i>	<i>Parvimonas.spp</i>	3.67	1.02E-02	0.29	0.10

	<i>chr5_112736443</i>	<i>Streptococcus.spp</i>	2.44	4.81E-02	0.09	0.60
	<i>chr10_87953776</i>	<i>C. hathewayi</i>	4.80	1.96E-02	0.24	0.17
<b>PTEN</b>	<i>chr10_87878155</i>	<i>A. segnis</i>	4.16	4.59E-02	0.14	0.44
	<i>chr10_87862867</i>	<i>A. segnis</i>	3.97	4.61E-02	0.14	0.44
	<i>chr13_27970216</i>	<i>C. hathewayi</i>	2.18	3.54E-06	0.18	0.31
	<i>chr13_27966667</i>	<i>C. clostridioforme</i>	1.59	4.61E-06	0.03	0.88
	<i>chr13_27970489</i>	<i>C. hathewayi</i>	1.35	1.88E-05	0.12	0.49
	<i>chr13_27966121</i>	<i>Ruminococcaceae</i>	1.98	2.66E-05	0.25	0.16
	<i>chr13_27966667</i>	<i>S. variabile</i>	1.20	1.41E-04	0.26	0.15
	<i>chr13_27967486</i>	<i>S. variabile</i>	2.52	2.08E-04	0.22	0.21
	<i>chr13_27969397</i>	<i>S. variabile</i>	1.90	2.72E-04	0.26	0.14
	<i>chr13_27967759</i>	<i>C. clostridioforme</i>	2.11	2.98E-04	0.11	0.55
	<i>chr13_27970762</i>	<i>C. clostridioforme</i>	3.11	4.17E-04	0.19	0.28
	<i>chr13_27968032</i>	<i>S. variabile</i>	1.16	5.68E-04	0.29	0.10
	<i>chr13_27965575</i>	<i>Mogibacterium</i>	7.07	1.44E-03	0.10	0.58
	<i>chr13_27969670</i>	<i>S. variabile</i>	1.61	1.62E-03	0.20	0.28
	<i>chr13_27971035</i>	<i>Streptococcus.spp</i>	0.98	1.82E-03	0.34	0.05
<b>CDX2</b>	<i>chr13_27966940</i>	<i>S. variabile</i>	1.30	1.98E-03	0.22	0.22
	<i>chr13_27969397</i>	<i>C. clostridioforme</i>	1.59	2.11E-03	0.02	0.90
	<i>chr13_27965302</i>	<i>C. clostridioforme</i>	5.72	2.89E-03	0.09	0.61
	<i>chr13_27967759</i>	<i>S. variabile</i>	1.93	3.25E-03	0.11	0.54
	<i>chr13_27969943</i>	<i>Streptococcus.spp</i>	2.42	4.99E-03	0.24	0.19
	<i>chr13_27968851</i>	<i>Ruminococcaceae</i>	1.39	5.88E-03	0.34	0.05
	<i>chr13_27970489</i>	<i>Streptococcus.spp</i>	0.70	6.25E-03	0.20	0.27
	<i>chr13_27966394</i>	<i>C. clostridioforme</i>	1.17	7.21E-03	0.35	0.05
	<i>chr13_27971035</i>	<i>C. hathewayi</i>	1.11	7.27E-03	0.11	0.55
	<i>chr13_27966394</i>	<i>S. variabile</i>	1.36	8.96E-03	0.25	0.16
	<i>chr13_27968851</i>	<i>S. variabile</i>	1.38	9.75E-03	0.34	0.05
	<i>chr13_27967759</i>	<i>B. plebeius</i>	2.33	1.14E-02	0.11	0.53
	<i>chr13_27966667</i>	<i>B. plebeius</i>	1.50	1.36E-02	0.12	0.51
	<i>chr13_27968578</i>	<i>Ruminococcaceae</i>	2.03	1.63E-02	0.35	0.05
	<i>chr13_27965848</i>	<i>C. clostridioforme</i>	1.70	2.24E-02	0.45	0.01

<i>chr13_27969943</i>	<i>S. variabile</i>	1.85	2.33E-02	0.15	0.40
<i>chr13_27966394</i>	<i>B. plebeius</i>	1.59	2.35E-02	0.23	0.20
<i>chr13_27970216</i>	<i>Streptococcus.spp</i>	0.87	2.36E-02	0.15	0.39
<i>chr13_27967213</i>	<i>S. variabile</i>	1.91	2.78E-02	0.05	0.79
<i>chr13_27967759</i>	<i>B. ovatus</i>	1.45	2.84E-02	0.04	0.80
<i>chr13_27970762</i>	<i>Streptococcus.spp</i>	1.26	3.13E-02	0.03	0.85
<i>chr13_27965302</i>	<i>S. variabile</i>	2.92	3.42E-02	0.46	0.01
<i>chr13_27968305</i>	<i>S. variabile</i>	0.85	3.81E-02	0.31	0.08
<i>chr13_27966121</i>	<i>S. variabile</i>	1.40	3.85E-02	0.13	0.47
<i>chr13_27968305</i>	<i>Ruminococcaceae</i>	0.92	4.17E-02	0.31	0.08
<i>chr13_27967486</i>	<i>B. plebeius</i>	2.05	4.72E-02	0.03	0.87

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